


Magnetic resonance imaging system for intraoperative margin assessment for DCIS and invasive breast cancer using the ClearSight™ system in breast-conserving surgery—Results from a postmarketing study

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Abstract

Background and objectives: Breast-conserving surgery (BCS) is followed by re-operations in approximately 25%. Reoperations lead to an increased risk of infection and wound healing problems as well as a worse cosmetic outcome. Several technical approaches for an intraoperative margin assessment to decrease the reoperation rate are under evaluation, some of them are still experimental.

Methods: A prospective single-arm post-marketing study with 60 patients undergoing BCS for ductal carcinoma in situ (DCIS) and invasive breast cancer was conducted. The specimen was intraoperatively examined by the ClearSight™ system, a mobile magnetic resonance imaging system that is based on a diffusion-weighted imaging protocol. However, the results were blinded to the surgeon.

Results: The ClearSight™ system was performed for both ductal and lobular breast cancer and DCIS, with a sensitivity of 0.80 (95% confidence interval [CI]: 0.44–0.96) and a specificity of 0.84 (95% CI 0.72–0.92), with an overall diagnostic accuracy of 80%.

Conclusion: Had the ClearSight™ been known to the surgeon intraoperatively, the reoperation rate would have been reduced by 83% for invasive carcinoma, from 10% to 2%, and 50% for DCIS, from 30% to 15% reoperations. A trial designed to examine the impact on reoperation rates is currently ongoing.

KEYWORDS

diffusion weighted, lumpectomy, re-excision rate, surgical margins

Abbreviations: ADC, apparent diffusion coefficient; BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; DW, diffusion weighted; IBC, invasive breast cancer; IOUS, intraoperative ultrasound; MR, magnetic resonance; MRI, magnetic resonance imaging; OCT, optical coherence tomography; ROC, receiver operating characteristic.

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1 | INTRODUCTION

Breast cancer is the most common invasive cancer in women worldwide, comprising 25.2% of invasive cancer in women and causing 14.2% of cancer deaths in women.¹

Breast-conserving surgery (BCS) is one of the most common procedures performed for the treatment of breast cancer. The aim of BCS is to remove the malignant tissue with clear margins, that is, with no ink on tumor for invasive breast cancer (IBC) and with a rim of normal tissue around it in ductal carcinoma in situ (DCIS). Achieving clear margins is important to decrease the risk of local recurrence, which is 2–3 times more frequent if lumpectomy margins are not clear.^{2–5} Reported positive margin rates after BCS for IBC and DCIS are 15%–47%^{6–9} and 20%–81%,^{10–16} respectively. Re-excision and completion mastectomy rates range between 23% and 59%.^{17–20} Reoperation for involved margins is associated with worse cosmetic outcomes, increased medical costs, and patient anxiety. Therefore, obtaining negative margins during primary BCS is essential. To date, there are a number of methods for the intraoperative assessment of surgical margins in DCIS and IBC, such as frozen section, specimen radiography, and intraoperative ultrasound (IOUS).²¹ Frozen section is very time-consuming, technically challenging since breast tissue is often fatty and hard to freeze and cut, requires evaluation by an experienced pathologist, thus, ranging sensitivity of 65%–78%.²² The use of radiographic X-ray mammography is limited due to limitations in detecting small noncalcific lesions and a high rate of nonspecific findings.²³ Specimen radiography found a sensitivity and specificity for detecting margin positivity of 49%–53% and 77%–84%, respectively.²⁴ IOUS is a well-known tumor localization technique. However, when used for margin assessment, it is less suitable for invisible lesions and microcalcifications detection,²⁵ found to have a sensitivity of 59% and a specificity of 81%.²⁶ Both imaging methods present a valuable addition to BCS.

However, intraoperative assessment of surgical margins in DCIS remains challenging and is an unmet need. Magnetic resonance imaging (MRI) was reported to be an accurate imaging technology for breast cancer detection, with high sensitivity compared with conventional techniques, and provides highly sensitive information on DCIS.^{27–29}

The novel ClearSight™ system (ClearCut Medical Ltd.), is a CE mark-approved intraoperative MRI-based device designed to assess surgical specimen margins in real-time.

The objective of this study is to evaluate the performance of the ClearSight™ system in assessing surgical margins for DCIS and IBC and assessing the ability of the ClearSight™ as an adjunct tool to reduce the re-excision rate following primary BCS.

2 | MATERIALS AND METHODS

2.1 | The ClearSight™ system

The ClearSight™ system is an intraoperative mobile MRI system, designed for real-time magnetic resonance (MR) measurement of excised breast tissue margins in the operating room.

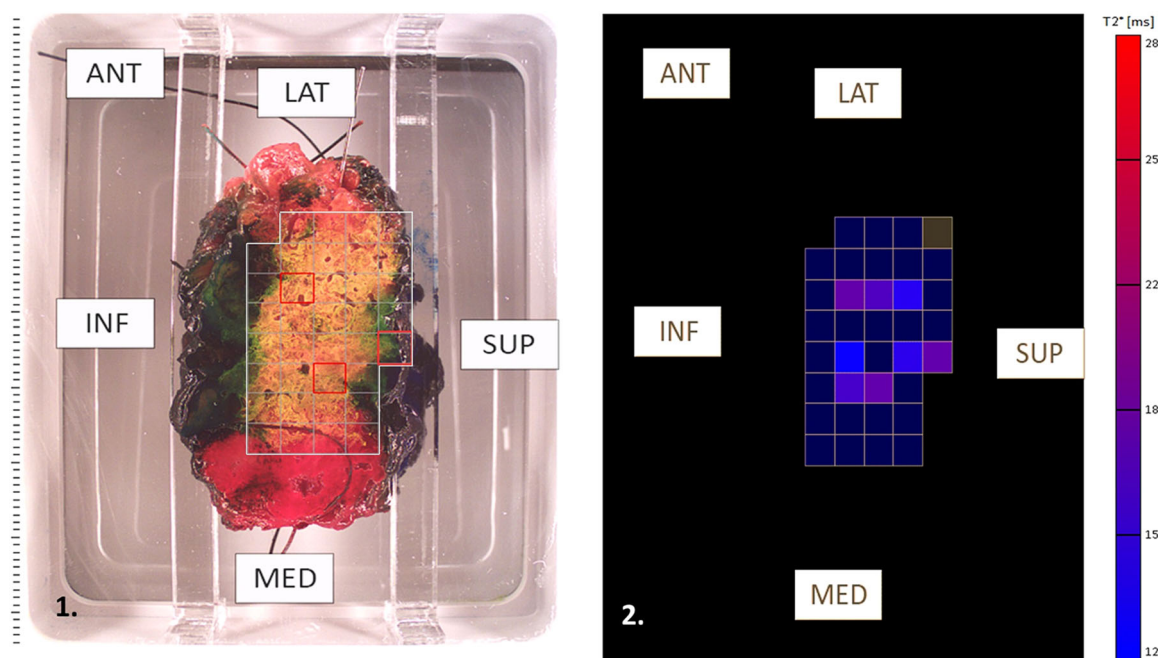
The system is based on a diffusion-weighted (DW) imaging protocol, which measures the random thermal Brownian diffusion of water molecules in the tissue. The rate of water diffusion is quantified by the apparent diffusion coefficient (ADC), which was shown to be a good differentiator parameter of malignant and benign breast tumors with a sensitivity of 93% and specificity of 88%.^{30,31} The ClearSight™ system measures the T-2 star (T2*) value, which has an inverse relationship between the cellularity and ADC, hence the ability to distinguish malignant and nonmalignant tumors in freshly excised breast tissue. The system scans a predefined 4 mm diameter and 1 mm thickness of the excised tissue surface and generates a two-dimensional color scale (Figure 1).

2.2 | Study design

The study was a prospective, single-arm, blinded postmarketing study that enrolled 63 patients. It was conducted at the Agaplesion Markus Hospital, following the approval of the institutional ethics committee. Each patient signed an informed consent form before enrollment in the study. Women over 18 years diagnosed with IBC or DCIS of the breast were included in the study. All patients were eligible for BCS, had no prior systemic neoadjuvant therapy, and had no prior breast surgery or implants. The BCS included a routine lumpectomy and criteria for re-excision were according to site and surgeon discretion using standard methods. No standardization between surgeons' surgical methods was required. All aspects of the freshly excised breast specimens were inked by the surgeon intraoperatively to uniquely define margin orientation for accurate comparison to final histopathology results. Following completion of the lumpectomy, that is, segmentectomy, multiple margins were scanned using the ClearSight™ system, generating a color-coded map of the T2* MR values, representing the tissue's DW properties (Figure 1). The ClearSight™ was operated by either site or ClearCut personnel. As the ClearSight™ system was used following the completion of the lumpectomy/segmentectomy. All medical staff members were blinded to the ClearSight™ results, and patient management was not affected by the MR findings. Following MR scans, the specimens were sent for standard histopathology and margin assessment evaluation including routine hematoxylin and eosin staining, as per site protocols. The pathologist was unblinded to the ClearSight™ system output, to sample further tissue depicted with high restricted diffusion properties and high T2* values. Final margin status for the main lumpectomy/segmentectomy specimen margins as reported in the pathology report was compared to the margin status as determined by the T2* MR values of the ClearSight™ system, allowing for evaluation of the system's performance to detect positive margins with a subsequent potential reduction of postoperative positive margins.

2.3 | Statistical analysis

The primary analysis was completed on all patients and specimen aspects with valid ClearSight™ outputs and corresponding histopathology assessments. Scans were classified as malignant or nonmalignant based



ClearSight™ system scans: 1. optical image of the fresh breast tissue with a defined scanned area (white). In red are marked the highest T2* values within the tissue. 2. a 2D color-coded magnetic resonance map (T2* values) .

FIGURE 1 ClearSight™ system scans: (1) Optical image of the fresh breast tissue with a defined scanned area (white). In red are marked the highest T2* values within the tissue. (2) A 2D color-coded magnetic resonance map (T2* values). 2D, two dimensional; ANT, anterior; INF, inferior; LAT, lateral; MED, medial; SUP, superior

on the MR signal as presented by calculated T2* values and scored according to the correlation with pathology findings ≤ 1 mm from the margin. The primary endpoint of the study was the ability of the ClearSight™ system to assess the presence of malignant findings within 1 mm from excised specimen margins, compared to the gold standard histopathology examination. The gold standard for margin assessment is histopathology, evaluating the microscopic distance from the tumor to each specimen margin and distinguish between tumor on-ink and a close margin. Nevertheless, there is no consensus and there is a lack of standardization in the pathological method regarding the definition of an adequate negative margin, thus followed by various patient management.

No ink on tumor for IBC is guided by the Society of Surgical Oncology and American Society of Radiation Oncology (SSO-ASTRO) guideline,³² while the Association of Breast Surgery United Kingdom (ABS-UK),³³ and the German Society for Gynecology and Obstetrics and the German Cancer Society refers to a clear margin at 1 mm from all sides of the tumor (Germany S3 guideline).^{34,35} As for pure DCIS, both the SSO-ASTRO and the German guideline encounter a clear margin at 2 mm, rather a 1 mm surgical margin by the ABS-UK.

As mentioned before, the ClearSight™ system can distinguish malignant and nonmalignant tumors in freshly excised breast tissue up to 1 mm depth.

Analysis of the results included ClearSight™ system accuracy performance over time, using Receiver operating characteristic (ROC) curve analysis with the entire range of T2* values measured in the study, and sensitivity and specificity calculations.

All continuous variables were presented as mean and standard deviation, whereas categorical values were presented by frequencies and percentages, when appropriate. All statistical analyses were two-tailed tests and significance was set at 5%. No missing data were imputed. Results were analyzed using SPSS version 23.0 (IBM, SSPS Inc).

3 | RESULTS

Sixty-three patients were enrolled in the trial between August 2017 and April 2018. Three patients did not meet inclusion criteria due to neoadjuvant therapy, formalin fixation before specimen scan, and inability to ascertain specimen margins (one each). From the 60 patients, the ClearSight™ system performed and analyzed a total of 348 scanned aspects (5.8 ± 0.5 scans per patient). The mean patient age was 61.2 years (36–80 years). Forty-two patients (70%) had invasive ductal carcinoma, four patients (7%) had invasive ductal carcinoma with DCIS, nine patients (15%) had pure DCIS, and five (8%) had invasive lobular carcinoma. The majority of tumors were either well (33%), or moderately (64%) differentiated. Patient demographics and preoperative tumor type are listed in Table 1. BCS procedures were performed by three surgeons. Extensions were taken in 35% of cases.

Mean calculated tumor volume (estimated by multiplying the three dimensions) was 3.1 ± 6.8 cc, and 52% (31/60) of the main lumpectomy/segmentectomy specimens contained at least one positive margin within 1 mm per histology. Of the 348 margins assessed, 15.5% (54/348) margins had a pathological finding, the majority

TABLE 1 Patient demographics and preoperative characteristics

Parameter	Value
Age <i>n</i> (%)	
Mean (STD)	61.2 (10.5)
<40	1 (2)
40–50	10 (17)
50–60	14 (23)
60–70	20 (33)
>70	15 (25)
Body mass index (kg/m ²), <i>n</i> (%)	
<18.5	8 (13)
18.5–25	27 (45)
25–30	22 (37)
>30	3 (5)
Tumor type, <i>n</i> (%)	
IDC	42 (70)
ILC	5 (8)
IDC with DCIS	4 (7)
DCIS	9 (15)
Tumor grade, <i>n</i> (%)	
I	20 (33)
II	38 (64)
III	2 (3)

Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

(9.5%) being DCIS, and 6.0% with invasive ductal carcinoma at the margin. Tumor characterization based on final pathology results is presented in Table 2.

The maximum ClearSight™ T2* value calculated for each specimen aspect and presented as a numerical output was 12.4 ± 5.7 ms for nonmalignant tissue and 16.7 ± 2.7 ms for malignant tissue. T2* was significantly different between the two groups ($p < 0.00001$). A ROC analysis, depicted in Figure 2, demonstrated the ClearSight™ performance had a sensitivity of 0.65 (95% confidence interval [CI]: 0.52–0.78) and specificity of 0.80 (95% CI: 0.75–0.85), with an overall diagnostic accuracy of 80%. When looking at different cancer types, the sensitivity for IBC and DCIS were 0.86 (95% CI: 0.71–1.00), and 0.52 (95% CI: 0.35–0.69), respectively. Out of these findings, there were seven IBC findings on-ink, of which six (86%) were detected by the ClearSight™ system (Table 3). The system performance difference between histopathology types was found to be affected by tissue dehydration which occurs over time from excision. When analyzing system capabilities within 1 h from specimen excision (67 scans), the diagnostic performance was shown to improve and

TABLE 2 Specimen and tumor characteristics

Parameter	Value
Specimen volume (cc)	
Mean (STD)	48.2 (31.1)
Specimen weight (g)	
Mean (STD)	20.1 (13.2)
Tumor volume (cc)	
Mean (STD)	3.1 (6.8)
Histology margin assessment (≤1 mm)	
Positive margins, <i>n</i> (%)	
IDC	13 (24)
ILC	6 (11)
IDC + DCIS	2 (4)
DCIS	32 (59)
ADH	1 (2)
Negative margins, <i>n</i> (%)	
	294 (84)

Note: The table presents histopathology data on the specimens.

Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

found to be the same for both histopathology subtypes, ductal and lobular IBC and DCIS, with a sensitivity of 0.80 (95% CI: 0.44–0.96) and specificity 0.84 (95% CI: 0.72–0.92). Anyway, there is no reason to wait longer than 1 h when intraoperative results are needed to continue the operation.

Data were further analyzed at the patient level. Results from all individual margins for a patient were compiled to yield the patient-level classification. For a patient with a positive specimen to be considered as “successfully detected,” it was required that all pathological positive margins on the specimen were detected. In 24 out of 60 (40%) patients, the initially excised specimens were positive by histopathology and were not addressed intraoperatively by tissue re-excision, resulting in postoperative referral for a re-excision BCS; this comprised 6 patients with pure IBC, 13 patients with DCIS at the margin, and 5 patients with both invasive and DCIS at the margin. Of these positive specimens, the ClearSight™ successfully detected five (83%) in whom margins were involved by invasive ductal carcinoma and nine (50%) of specimens with DCIS at the margin. These detection rates characterize ClearSight™ system diagnostic performance at the per-margin and per-patient levels. Overall, had the ClearSight™ been used intraoperatively, the reoperation rate would have been reduced by 83% for invasive carcinoma, from 10% to 2%, and 50% for DCIS, from 30% to 15% reoperations.

Accordingly, the ClearSight™ could provide useful adjunctive intraoperative inputs and guide decision-making, with respect to surgical margin adequacy, and contribute to improved patient outcomes.

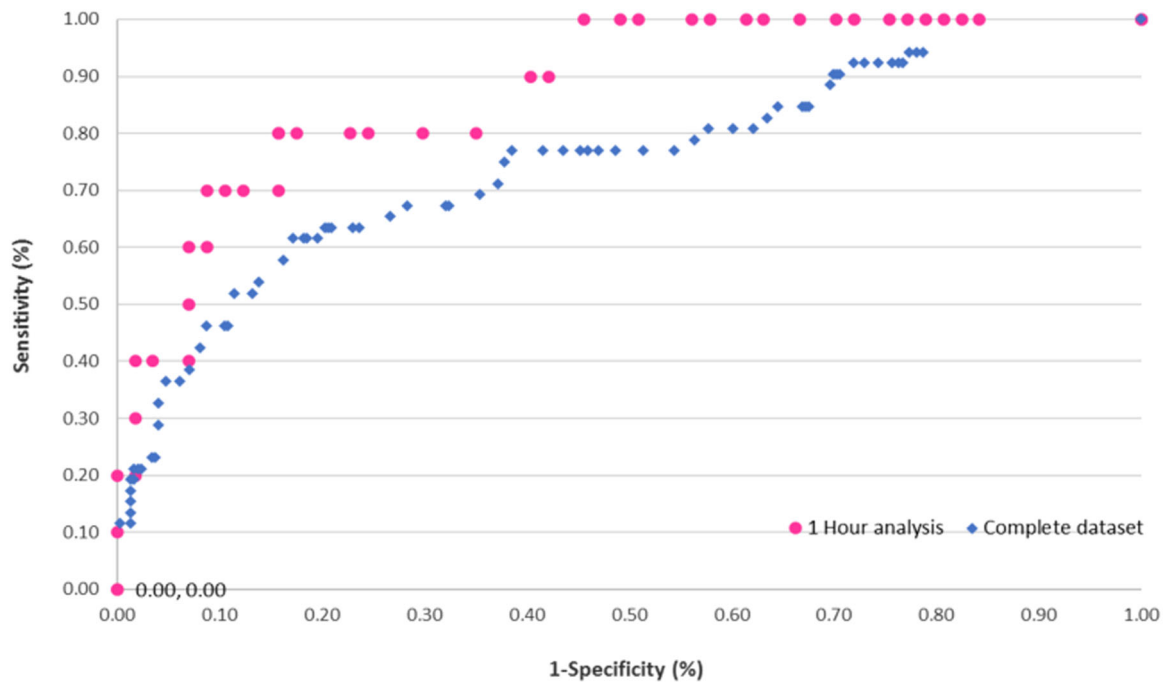


FIGURE 2 Receiver operating characteristics (ROC) curve of ClearSight™ performance (all histological subtypes). ROC curve of two different datasets: (1) complete dataset containing all samples (squares) and (2) samples scanned within 1 h from specimen excision (circles)

TABLE 3 Device detection rate for tumor at the margin by histological subtypes

Cancer histopathology	Number of samples (n)		Detected samples (n)		Detection rate (%)	
	≤1 mm	On-ink	≤1 mm	On-ink	≤1 mm	On-ink
Invasive cancer						
IDC	13	6	11	6	85	100
ILC	6	1	5	0	83	0
IDC + DCIS	2	0	2	NA	100	NA
All	21	7	18	6	86	86
Noninvasive cancer						
DCIS, ADH	33		17		52	

Note: The table presents a number of histology positive margins per subtypes and the corresponding margins detected by the ClearSight™ system.

Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

4 | DISCUSSION

Real-time intraoperative margin assessment in BCS continues to pose a challenge, with positive margin rates requiring relumpectomy in the range of 11%–46%.³⁶ Novel technologies for intraoperative margin assessment are being explored, and several technologies are in various stages of development and testing.

We report herein on the results of the ClearSight™ system and have demonstrated a sensitivity and specificity of up to 80% and 84%, respectively. These results are in concordance with the results of a previously published study,³⁷ which showed that DW MRI is a valid technology for the assessment of tumors in freshly excised tissue. The prior study examined 6 mm sections of breast tissue after

surgery and found a sensitivity and specificity of 91% and 93%, respectively. In the current study, we measured whole aspects of entire specimens and found a somewhat lower sensitivity and specificity, attributable to the fact that an entire surface was scanned, which is more heterogeneous in terms of types of tissue compared to a small (6 mm) sample. However, despite the compound tissue types at the surface of a whole specimen, the ClearSight™ system was able to differentiate benign from malignant tissue with a high level of accuracy (84%).

Other technologies which are being developed for the same purpose include radio frequency (RF) spectroscopy, bioimpedance spectroscopy, fluorescence molecular imaging, and technologies-based optical coherence tomography (OCT).

RF spectroscopy is the technology used by the MarginProbe[®], and in several clinical and postmarketing trials has been shown to reduce reoperation rate by 56% but suffered from low specificity with a 53.6% false-positive rate.^{38,39} The procedure involves an examination of the specimen by a handheld probe which samples a 7 mm area in each measurement, in under 1 s. Sensitivity and specificity are reported in the range of 71% and 68%, respectively.^{40,41}

Bioimpedance spectroscopy⁴² measures dielectric tissue properties on the freshly excised lumpectomy specimen and can differentiate fatty and fibrotic breast tissue from tumors. In one reported trial, the device had a sensitivity of 87.3%, specificity of 75.6%, and the potential to decrease reoperation rate from 37% to 7%.

Fluorescence molecular imaging, or Cerenkov luminescence imaging, uses positron emission tomography of the specimen after injecting patients intravenously with 18F-fluorodeoxyglucose before surgery. In a preliminary report on 22 patients, the procedure was demonstrated to be safe and potentially effective in assessing lumpectomy margins during surgery. However, this technology relies on preoperative systemic administration of exogenous radioactive dye creating potential barriers to clinical implementation.⁴³

OCT, a novel technique capable of high-resolution imaging without a contrast agent, uses interferometry, creating an image based on the amount of backscattered light, with microscopic resolution. Preliminary studies have reported a high sensitivity in the range of 80%–94%, and a specificity of 87%–93% for detecting cancer in mastectomy specimens,^{44–46} and sensitivity of 55%–65% and specificity of 68%–70%⁴⁷ in BCS, which may be related to the limited ability of the OCT or optical coherence micro-elastography to distinguish between tumor and surrounding normal stroma.⁴⁸ Additional OCT-based technologies yielded a sensitivity of 91.7% and specificity of 92.1% following wide local excision of 35 human breast tumors.⁴⁴

In the current study, a full evaluation of almost the entire surface of the excised specimen was performed by DW MRI scanning and compared to the histopathological findings meticulously.

The advantage of the ClearSight™ system is that it uses well-established technology for the characterization of tissue, offers full-surface scanning, and does not require to expertize in X-ray interpretation or pathology evaluation. The system can be operated by the regular operation room staff with minimal training.

5 | CONCLUSION

Our results suggest that the ClearSight™ system has the potential to reduce reoperation rates by up to 80% for patients undergoing BCS when used at the time of surgery on freshly excised tissue.

This study is limited by the fact that findings were not communicated back to the surgeon and were not actionable, and, therefore, did not influence intraoperative decision-making regarding excising additional tissue.

Evaluation of the technology in a trial designed to examine the impact on reoperation rates is currently ongoing and will establish the utility of the ClearSight™ system in clinical practice. A clinical trial

would also need to assess the impact of the logistics of specimen orientation and scanning on operative time and workflow in the operating room.

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CONFLICT OF INTERESTS

Marc Thill received honoraria for advisory boards from ClearCut, Norgine, Neodynamics, pfm medical, RTI Surgical, and Sysmex; manuscript support from ClearCut and pfm medical; travel reimbursement from Medtronic, Norgine, pfm Medical, and RTI Surgical; and lecture honoraria from Medtronic, pfm medical, and RTI Surgical. Iris Szwarcfiter is a Clear-Cut employee and has a financial interest in the company. Katharina Kelling received honoraria for advisory boards from pfm medical. Eyal Kolka is a Clear-Cut's Innovator and has a financial interest in the company. Zachi Peles is a Clear-Cut employee and has a financial interest in the company. Moshe Papa is a Clear-Cut consultant and has a financial interest in the company. Vivane van Haasteren, Josefa Noelke, Sebastian Aulmann, and Tanir Allweis declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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